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13. ABSTRACT (Maximum 200 Words)
Prevention may represent a feasible approach to decreasing ovarian cancer mortality. To achieve a better understanding of the etiology of ovarian cancer, which can then be translated into more effective prevention strategies, we have initiated a molecular epidemiologic study in North Carolina that considers genetic susceptibility, reproductive/hormonal and other exposures and acquired genetic alterations. This case-control study is population-based with subjects recruited from 48 counties of central North Carolina. Subjects are interviewed in their homes, and about 350 cases and 400 controls have been accrued thus far. Blood and cancer samples have been collected and molecular analyses of p53, HER-2/*neu*, c-*myc* and genetic polymorphisms (eg. progesterone receptor) have commenced. We also have initiated an ovarian cancer chemoprevention program focusing on the progesterone receptor. Progestins have a potent apoptotic effect on ovarian epithelial cells and we have shown that levonorgestrel dramatically decreases ovarian cancer incidence in a chicken chemoprevention trial. In addition, we have shown that progestin mediated apoptosis in the ovarian epithelium is mediated by transforming growth factor-beta. We will continue to work towards an understanding of the molecular epidemiology of ovarian cancer and towards development of effective chemoprevention strategies that might decrease mortality from this disease.

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Introduction

Ovarian cancer is the fourth leading cause of cancer deaths among women in the United States. There are three potential approaches to decreasing ovarian cancer mortality: screening and early detection, more effective treatment and prevention. All of these avenues should be explored, but we believe that prevention represents the most feasible approach. The rationale for prevention is derived from epidemiologic studies that have examined the relationship between reproductive history, hormone use and ovarian cancer. It has been convincingly demonstrated that reproductive events which reduce lifetime ovulatory cycles are protective. Although most women are unaware of this protective effect, those who use oral contraceptive pills for more than 5 years or have 3 children decrease their risk of ovarian cancer by greater than 50%. The biological mechanisms that underlie the association between ovulation and ovarian cancer are poorly understood, however.

Our multidisciplinary ovarian cancer research group has been actively involved in studies that seek to elucidate the etiology of ovarian cancer and to translate this knowledge into effective preventive strategies. Joint consideration of genetic susceptibility, reproductive/hormonal and other exposures, acquired alterations in oncogenes and tumor suppressor genes and protective mechanisms such as apoptosis is required to accomplish this goal. We have initiated a molecular epidemiologic study of ovarian cancer in North Carolina to address the complex etiology of ovarian cancer.

In addition, we are actively involved in development of chemopreventive strategies. We have performed a study in primates that suggests that the oral contraceptive has a potent apoptotic effect on the ovarian epithelium, mediated by the progestin component. In addition, in subsequent studies performed *in vitro*, we have induced apoptosis in epithelial cells treated with the progestin levonorgestrel. Progestin mediated apoptotic effects may be a major mechanism underlying the protection against ovarian cancer afforded by OCP use. This forms the basis for an investigation of the progestin class of drugs as chemopreventive agents for epithelial ovarian cancer. Currently studies to test the progestin levonorgestrel are underway in chickens. In addition, we are exploring the molecular pathways that mediate progestin induced apoptosis in the ovarian epithelium.

Body

Projects 1 and 2: Molecular-epidemiology of ovarian cancer

With the support of the Department of Defense Ovarian Cancer Research Program we have initiated a molecular epidemiologic study of ovarian cancer to work towards the goal of a better understanding of the etiology of ovarian cancer. Drs. Andrew Berchuck (Gynecologic Oncologist) and Joellen Schildkraut (Epidemiologist) are working together to lead this study. Our initial plan was to accrue frozen tumor tissue and blood from 500 epithelial ovarian cancer cases treated at Duke University, the University of North Carolina at Chapel Hill and East Carolina University. In addition, 500 age and race-matched control subjects were to be accrued and both cases and controls were to be interviewed by telephone regarding known risk factors for ovarian cancer. After funding

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to support this project was received from the Department of Defense with Dr Berchuck as PI, additional funding was received to support this project from the NCI with Dr Schildkraut as PI. The additional funding has allowed us to increase the scope of the study such that nurse interviewers are visiting the homes of all the cases and controls to administer the study questionnaire. Research subjects are accrued from a 48 county region of central North Carolina using a rapid cases ascertainment mechanism established through the state tumor registry. Prior to initiating the study, we had to go through the process of IRB approval in each of the various hospitals involved. Treating physicians are contacted by mail to request permission to approach potential research subjects. A letter is sent inviting a woman to participate only if permission to contact is granted. Three nurse interviewers have been hired and trained and the research questionnaire was field tested on 20 women with ovarian cancer. Final revisions to the questionnaire were made before the study began to accrue actual research subjects. To date about 350 women with newly diagnosed ovarian cancer and 400 controls have been accrued in the study. The investigators have had project meetings every other week with all the research staff to review progress and address ongoing issues and at this point we are pleased with the accrual rate and other procedural aspects of the study. All clinical, epidemiologic and molecular data are stored as they are obtained in a computerized database.

During the interview a thorough history of the menstrual cycle and reproductive experiences of the study participants is obtained assisted by the use a life-time calendar method. In addition, information on oral contraceptives and hormone replacement therapy is obtained. Data on the family history of cancer, other risk factors, and potential confounders is also collected. The interview takes 60-90 minutes to complete. The interactions between the nurses and subjects has been uniformly positive (see newsletter in appendix). The women with ovarian cancer are highly motivated to talk about their history and have a high level of interest in supporting a study aimed at increasing our understanding of the causes of ovarian cancer. They greatly appreciate the opportunity to talk with a nurse who is truly interested in hearing all the details of their life experience.

Previously, using ovarian cancer cases and controls from the CASH study, we found a strong association between high lifetime ovulatory exposure and alteration of the p53 tumor suppressor gene. In project 1 of this proposal, directed by Dr. Berchuck (Gynecologic Oncologist), we are seeking to confirm the association between high lifetime ovulatory exposure and alterations in p53. More broadly, we will attempt to demonstrate that alterations in specific genes (eg, p53, HER-2/*neu*, c-*myc*) serve as molecular signatures of distinct etiologic pathways and allow definition of more homogenous subsets of ovarian cancer. This could be critical as we strive to develop prevention strategies, as the optimal means of prevention may vary between different subsets of these cancers. Ovarian cancer tissues have been collected and molecular analyses of the p53 tumor suppressor gene and HER-2/*neu* and c-*myc* oncogenes have recently commenced. In cases in which fresh frozen ovarian cancer tissue is not available, consent has been obtained to procure paraffin blocks. In the next few months we will merge the molecular and epidemiologic data from the first three hundred cases. This will allow us to address the goals of the specific aims outlined in this project

involving definition of distinct subsets of ovarian cancer through their underlying molecular signatures.

In project 2, initially under the direction of Dr. Futreal (Molecular Geneticist), we are examining the role of genetic susceptibility in the development of ovarian cancer. More recently, Dr. Futreal has left Duke and this project is now being led by Jeffrey Marks, Ph.D. (Molecular Biologist). Drs. Berchuck and Marks are co-directors of the Duke Comprehensive Cancer Center Breast/Ovarian Cancer Program and have a long track record of scientific collaboration over the past 10 years. Although most of the genes responsible for dominant hereditary ovarian cancer syndromes (eg. BRCA1/2) likely have been discovered, there is evidence to suggest that polymorphisms in other genes may also affect cancer susceptibility in a more weakly penetrant fashion. Dr. Marks will investigate whether genetic polymorphisms affect ovarian cancer susceptibility. These studies will focus on genes involved in pathways implicated in the development of ovarian cancer - such as hormone receptors. Since the effect of cancer susceptibility genes may be modified by other genes and exposures, he also will determine whether gene-gene and gene-environment interactions affect ovarian cancer susceptibility. Because of the low incidence of ovarian cancer, the ability to identify "high risk" subsets of women is critical if we hope to translate our emerging understanding of the etiology of ovarian cancer into effective prevention strategies.

It has been postulated that decreased activity of the progesterone receptor and vitamin D receptor or increased activity of the androgen receptor might increase OC risk. In view of this, we performed analyses of genetic polymorphisms in 301 cases (75% invasive, 25% borderline) and 358 controls in the North Carolina Ovarian Cancer Study. PCR-based methods were used to examine allele frequencies of polymorphisms in the progesterone receptor (PROGINS), vitamin D receptor (exon 9 Taq1 RFLP) and androgen receptor (exon 1 CAG repeat). Odds ratios (ORs) were computed and associations between genotypes and case/control status were assessed using logistic regression adjusting for age and race. There were no differences between cases and controls in mean age (54.0 years vs. 54.7 years) or fraction of African Americans (11% vs 14%). For the progesterone receptor polymorphism, ORs were 1.2 for heterozygotes (95% CI 0.8-1.7) and 0.8 for homozygotes (95% CI 0.4-1.8). For the vitamin D receptor polymorphism, ORs were 1.4 for heterozygotes (95% CI 1.0-2.0) and 1.1 for homozygotes (95% CI 0.7-1.8). The size of this study provides 80% power to detect ORs of 1.6 at a p=0.05 2-sided level. For the CAG polymorphism in the androgen receptor, there was no difference in mean allele lengths between cases (20.8 repeats) and controls (20.7 repeats). In addition, the frequency of either very long ($\geq$27) or a very short CAG alleles ($\leq$16) did not differ between cases and controls. None of the three polymorphisms were associated with age of OC onset or borderline vs. invasive histology. This study is not supportive of the hypothesis that polymorphisms in the progesterone receptor, vitamin D receptor or androgen receptor affect OC risk. We are also collecting epidemiologic data and in the future will examine whether nulliparity or other known risk factors are modified by these polymorphisms. The identification of polymorphisms that increase OC risk is a worthwhile endeavor as this could facilitate

identification of high-risk women who would be candidates for screening and/or prevention interventions designed to decrease mortality.

Project 3: chemoprevention

Project 3 is under the direction of Gustavo Rodriguez, M.D. (Gynecologic Oncologist). The prevention strategy outlined in our proposal is based on the observation that progestins have a potent apoptotic effect on ovarian epithelial cells. With regard to cancer prevention, the apoptosis pathway is one of the most important *in vivo* mechanisms that functions to eliminate cells that have sustained DNA damage and which are thus prone to malignant transformation. In addition, a number of well known chemopreventive agents have been demonstrated to activate the apoptosis pathway in the target tissues that they protect from neoplastic transformation. We have performed a study in primates that suggests that the oral contraceptives (OCs) have a potent apoptotic effect on the ovarian epithelium, mediated by the progestin component. In addition, in subsequent studies performed *in vitro*, we have induced apoptosis in transformed, immortalized, cultured human ovarian epithelial cells treated with the progestin levonorgestrel. This suggests that progestins may have a direct apoptotic effect on the ovarian epithelium. The finding that progestins activate this critical pathway in the ovarian epithelium, the site where ovarian cancers arise, makes it likely that progestin mediated apoptotic effects are a major mechanism underlying the protection against ovarian cancer afforded by routine OC use. This forms the basis for an investigation of the progestin class of drugs as chemopreventive agents for epithelial ovarian cancer.

The studies outlined in our prevention grant are designed to add further support to notion that progestins are potent apoptotic agents on human ovarian epithelial cells, and to directly test the hypothesis in an animal model that progestins confer preventive effects against ovarian cancer. These aims in the grant are: (1) to evaluate the apoptotic effect of progestins on the human ovarian epithelium *in vivo*, (2) elucidate the molecular mechanisms by which progestins induce apoptosis in ovarian epithelial cells, and (3) to directly test the hypothesis that progestins confer preventive effects against ovarian cancer in a chemoprevention trial in the chicken, the only animal species with a high incidence of ovarian cancer.

In search of biologic effects of OCs that have the potential to confer protective effects against ovarian cancer, we performed a 3-year study in primates that suggests that oral contraceptive progestin markedly induces programmed cell death (apoptosis) in the ovarian epithelium and that this is highly associated with up-regulation of Transforming Growth Factor-Beta (TGF-β). These two molecular events have been strongly implicated in cancer prevention *in vivo*, and are believed to underlie the protective effects of other well-known chemopreventive agents such as the retinoids and Tamoxifen. In subsequent studies performed *in vitro*, we have induced apoptosis in immortalized, cultured human ovarian epithelial cells treated with progestin suggesting that progestins may have a direct apoptotic effect on the ovarian epithelium. We have completed a two-year prevention trial in the chicken (the only known animal with a high incidence of spontaneous ovarian adenocarcinoma) designed to test the hypothesis that progestins confer prevention against ovarian cancer. Two thousand two year-old birds were randomized into several groups,

including untreated controls, and groups receiving progestin (Provera or levonorgestrel). Preliminary results suggest that at the two-year mark, chickens in groups treated with progestin contained 35% fewer ovarian and oviductal tumors than controls.

Given our preliminary data, we hypothesize that OC progestins induce apoptosis in the human ovarian epithelium, and that induction of apoptosis is possibly mediated by TGF-β. With regard to cancer prevention, the apoptosis pathway is one of the most important *in vivo* mechanisms that functions to eliminate cells that have sustained DNA damage and which are thus prone to malignant transformation. In addition, a number of well-known chemopreventive agents have been demonstrated to activate the apoptosis pathway in the target tissues that they protect from neoplastic transformation. The finding that progestins activate this critical pathway in the ovarian epithelium raises the possibility that progestin-mediated apoptotic effects underlie the protection against ovarian cancer afforded by routine OC use rather than inhibition of ovulation as has been previously suggested. This forms the basis, in our opinion, for further investigation of progestins as chemopreventive agents for ovarian cancer.

Key research accomplishments

We have gathered significant pre-clinical evidence in support of progestins as potential ovarian cancer preventive agents. Our research is now extending to the evaluation of other candidate agents for the prevention of ovarian cancer.

1) We have discovered that progestins markedly activate TGF-β signaling pathways in the ovarian epithelium in primates, and that these effects are highly associated with apoptosis. We are now performing studies *in vitro* designed to characterize the complex biologic effects of progestins and other candidate preventive agents on apoptotic and TGF-β signaling pathways in ovarian epithelial cells, and seek to determine whether TGF-β mediates the apoptotic effect of progestins on the ovarian epithelium.

2) Our avian chemoprevention trial has been completed. An avian patholgist and gynecologic pathologist have been performing a meticulous evaluation of the tumors accrued during the trial. Our preliminary data suggests a 35-50% reduction in reproductive tract tumors in our progestin-treated chickens as compared to appropriate controls. In addition, we have some evidence that the combination of a Vitmain D-enriched diet and progestin treatment might have enhanced ovarian cancer preventive effects over progestin alone.

3) We have performed a reanalysis of data from the Cancer and Steroid Hormone Study (CASH), leading to the finding that progestin-potent oral contraceptives confer enhanced protection against ovarian cancer as compared to progestin-weak oral contraceptives. These are the first human data directly linking the progestins in oral contraceptives to an ovarian cancer protective effect.

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Reportable outcomes

1) Progestin induction of apoptosis in the macaque ovarian epithelium is associated with differential regulation of transforming growth factor-β.

2) Combination OC formulations with high progestin potency may confer greater protection against ovarian cancer than those with low progestin potency.

Conclusions

The studies initiated by our program will enable us to define more homogeneous subsets of ovarian cancer based on epidemiologic and molecular characteristics, to identify women who are at increased risk for this disease and to develop chemopreventive strategies designed to decrease ovarian cancer incidence and mortality. We anticipate that much of our data will grow to maturity in coming year.

References

1) Rodriguez GC, Nagarsheth N, Rex C. Bentley, Walmer DK, Cline M, Whitaker RS, Eisner P, Berchuck A, Dodge R, Adams M, Hughes CL: Progestin Induction of Apoptosis in the Macaque Ovarian Epithelium is Associated with Differential Regulation of Transforming Growth Factor-Beta. J Natl Cancer Inst (in press)

2) Schildkraut J, Caligert B, Rodriguez GC. The Impact of Progestin and Estrogen Potency of Oral Contraceptives on Ovarian Cancer Risk. J Natl Cancer Inst (in press)

3) Rodriguez GC, Carver D, Anderson K, Barnes J, Berchuck A, Whitaker R, Eisner P, Petitte J. Evaluation of Ovarian Cancer Preventive Agents in the Chicken. (Abstract) 2001 Annual meeting of the Society of Gynecologic Oncologists (best poster award)

4) Berchuck A, Lancaster J, Calingaert B, Wenham R, McLean K, Halibi S, Marks J, Schildkraut J. A case-control study of candidate ovarian cancer susceptibility polymorphisms. (Abstract) 2002 Annual meeting of the Society of Gynecologic Oncologists (submitted).

Appendices
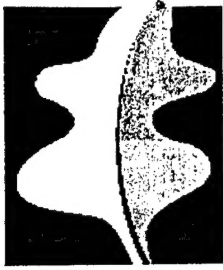
North Carolina
Ovarian Cancer Study

PURPOSE OF STUDY:

To identify the environmental, reproductive, and genetic factors that contribute to the development of ovarian cancer.

STUDY PERIOD:
1999-2003

STUDY ELIGIBILITY CRITERIA:

Diagnosis of primary epithelial ovarian cancer (including borderline) or primary peritoneal cancer;

Patient must be between the ages of 20 and 74 at diagnosis;

Patient must reside within 48-county study region (see map on p.3).

Out and About...

The *North Carolina Ovarian Cancer Study* is a multidisciplinary effort that involves a dedicated team of epidemiologists, gynecologic oncologists, molecular biologists, statisticians and nurses. In addition to working on a large population-based molecular epidemiologic study of ovarian cancer in our state, team members have been actively involved in a number of other activities over the past six months in the scientific community and the general community at large.

Andrew Berchuck

Dr. Andrew Berchuck has given presentations on early diagnosis and treatment of ovarian cancer as well as the management of hereditary ovarian cancer. Most notably, Dr. Berchuck served as the Program Chair for the 32nd Annual Meeting of the Society of Gynecologic Oncologists in Nashville, Tennessee. At this meeting, **Dr. Joellen Schildkraut** presented data that supported the hypothesis that oral contraceptive formulations with high progestin potency may confer greater protection against ovarian cancer. **Dr. Gus Rodriguez** presented data that supported an association between progestin induction of apoptosis (programmed cell death) in ovarian epithelium of macaque monkeys and up-regulation of a growth inhibitor named transforming growth factor-beta. Together, these studies support the hypothesis that progestin is an important component of the protective effect of oral contraceptives against the development of ovarian cancer. These abstracts were published in *Gynecologic Oncology* 80(2):275-276, 2001.

Joellen Schildkraut

Gus Rodriguez

Dr. Marilyn Vine served as a consultant on a grant application submitted to the American Cancer Society by the Piedmont Ovarian Cancer Association to support ovarian cancer awareness activities. She also served as a consultant to the North Carolina Advisory Committee on Cancer Coordination and Control regarding a document about early detection of ovarian cancer.

Nurses **Toya Hobbs**, **Robin Berger**, and **Nancy Fisher** and project manager **Mary Beth Bell** attended the Fall 2000 meeting of the Association of North Carolina Cancer Registrars where they displayed study information and spoke with cancer registrars from across the state.

NOTE: We would welcome any opportunity to discuss the *North Carolina Ovarian Cancer Study*. Please let us know if you would like us to provide information about the study at upcoming meetings or seminars.

NCOCS Accrual Report March, 2001

Recruitment Tally

Chart: Recruitment Tally. Y-axis 0 to 700. End of Study Goal line at ~700. Cases bar shows 264; Controls bar shows 270. A value of 111 appears in the Controls "In Progress" section. Legend: ■ In Progress, □ Completed Interviews. X-axis labels: Cases, Controls.

HIGH Study Interest Among Cancer Patients!

Thanks to the Gynecologic Oncologists and Cancer Registrars in hospitals in our study area who are participating in rapid-case ascertainment of newly diagnosed ovarian cancer cases, we continue to have great success in accruing study participants into the *North Carolina Ovarian Cancer Study*. Our **90% response rate** demonstrates the strong interest women have in participating in this study! We are making good progress toward our overall goal of completing 700 cases over the four-year period from January 1999 through December 2002 (see chart).

Active Consent Still a Hindrance

One of the biggest impediments to overall study accrual has been the low number of referrals from hospitals requiring "active" consent. In hospitals where cancer patients are required to return signed consent forms to the registrar before their name is released to the *NCOCS*, only 35-61% of women are returning signed consent. However, **when hospitals choose to call for consent rather than send letters, 100% of women contacted have agreed to learn more about the study!**

Thank You!!

We appreciate the efforts of all cancer registrars helping us out in this study, and particularly those in "active" consent hospitals who go the "extra mile" to get consent from patients. We are in the process of working with registrars and IRB's in "active" consent hospitals to facilitate effective ways to raise response rates. As our study continues, we will make every effort to assist all registrars in their efforts to help us accrue ovarian cancer patients into the study.

The oak leaf, with softened edges reflective of a female silhouette, is *the North Carolina Ovarian Cancer Study* logo. We have designed a small lapel pin depicting our logo to leave with participants in appreciation for their allowing us to enter their homes and lives for a short time to collect personal information for our research. With each pin we supply a small card expressing our gratitude to these extraordinary women.

The oak leaf,
The female silhouette.
Images of strength and endurance,
Two lasting qualities in the women we've met.

Thank you for your support.
The North Carolina Ovarian Cancer Study
1-888-246-1250
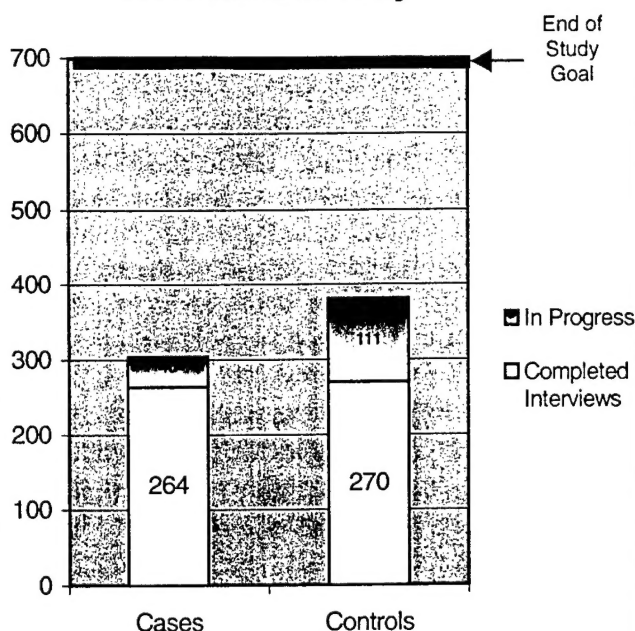
New Study to Characterize Symptoms of Ovarian Cancer

Dr. Marilyn Vine, an epidemiologist at the Duke University Medical Center, is heading up a small pilot study to better characterize patterns of symptoms associated with ovarian cancer.

The goal is to identify similarities and differences in symptoms between women with ovarian cancer and women with diseases that have symptoms similar to ovarian cancer such as irritable bowel syndrome and benign gynecologic conditions.

Better recognition of the signs and symptoms of ovarian cancer could lead to earlier diagnosis of some cases and this might improve survival. According to the American Cancer Society, 5-year survival for all stages of ovarian cancer is less than 50%. Survival for women with early, localized disease can be as high as 95%. However, most women are diagnosed with late stage disease (stages III/IV) where survival rates are less than 30%.

One reason women are often diagnosed late in the course of the disease is because there are currently no effective ways to screen women for ovarian cancer. Since the ovaries are located deep in the body, they can be difficult to feel. Laboratory tests are expensive and sometimes indicate the presence of the disease when the disease is not present, resulting in many unnecessary surgeries.

Another possible reason for late stage diagnoses is that women may not be aware of the seriousness of their symptoms, and therefore, delay seeking medical attention. Most women know the signs and symptoms of the more common cancers such as breast and colon cancer. Few women know what to look for when it comes to ovarian cancer, yet, most women are diagnosed with ovarian cancer because of symptoms. Most women have at least one symptom. Sometimes women are diagnosed during a routine pelvic examination or because of medical treatment for an unrelated condition.

Because the symptoms of ovarian cancer are similar to those of more common and less serious diseases/conditions, delays in diagnosis can also occur if health care providers do not consider the possibility that symptoms might be the result of ovarian cancer, and therefore, do not order the appropriate tests. Besides a pelvic exam, tests used to diagnose ovarian cancer include an ultrasound or CT Scan and a CA125 blood test. The diagnosis is confirmed with surgery.

Symptoms associated with ovarian cancer (which can be similar to those of more common and less serious conditions) may include:

- Persistent gas, nausea, indigestion
- Increased frequency or urgency of urination (or in some women, difficulty urinating) in the absence of infection
- Irregular bowel activity, such as diarrhea or constipation
- Unexplained weight gain or loss, particularly weight gain in the abdomen
- Pain during intercourse
- Pelvic or abdominal discomfort, such as heaviness, pressure or pain
- Bloating or feeling of fullness
- Abnormal menstrual or vaginal bleeding or discharge
- Loss of appetite
- Ongoing fatigue
- Distended or hard abdomen
- Difficulty breathing
- Palpable lump/mass in abdomen
- Backache
- Swollen legs or ankles
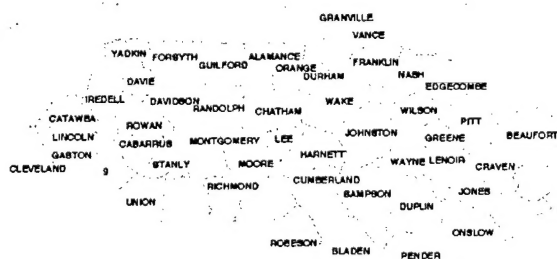
Marathon Fundraiser a Big Success!! $ $ $

In our last newsletter we told you about how Nurse-Interviewer Nancy Fisher, moved by the strength and courage of the many women she has met through the *NCOCS*, joined forces with the Piedmont Ovarian Cancer Association (POCA) and created the POCA Hope Fund. One hundred percent of money raised for the Hope Fund will be used to help North Carolina's ovarian cancer patients and their families who are experiencing financial hardships.

Nancy decided to run a marathon (even though she doesn't consider herself "a runner") to jumpstart her fundraising efforts. Although she originally planned to run the "1st Annual Fulcrum Marathon" in Raleigh on December 3, 2000, this race was postponed due to snow and rescheduled for a day that Nancy would be out of town. Determined not to give up, Nancy put in almost *2 more months* of training and completed the Charlotte "Run for Peace" marathon on January 27th of this year. All her hard work and training paid off—to date, donations for the Hope Fund have reached over $7,000!!! The POCA Board of Directors is currently setting up guidelines for how the funds will be disbursed.

Nancy reported that the 26.2 mile event went well. "I finished in 5 hours and 42 minutes, which is no record breaking time, but I was happy to finish in one piece! A sore piece, but one piece, nonetheless!" Nancy said that for each mile she ran she focused on a different ovarian cancer patient. "Running with a specific ovarian cancer patient in mind gave me great inspiration throughout the race. When I felt tired and ready to stop, I would think about the courage and strength that the ladies with ovarian cancer have shown, and I would get a boost of energy and get the push I needed to keep going for the finish line."

The Hope Fund will continue to accept contributions. For more information, please contact Nancy Fisher, RN, at 1-888-246-1250, or by e-mail at fishe002@mc.duke.edu. **Tax deductible contributions made payable to the Piedmont Ovarian Cancer Association can be sent to:**

Nancy Fisher
Box 2949 DUMC
Durham, NC 27710

Study Participation—How It Works

- The hospital Cancer Registrar sends monthly information on newly diagnosed ovarian cancer cases to the North Carolina Central Cancer Registry. (If needed, a representative from the Central Cancer Registry can assist with this task).

- The Central Cancer Registry forwards potentially eligible cases to the study project manager for determination of study eligibility.

- A consent form is sent to the attending physician requesting permission to contact their patient.

- When physician consent is received, a letter and brochure describing the study are sent to the patient.

- Shortly thereafter, a nurse-interviewer telephones the patient to discuss the study, determine eligibility, and, if eligible, invite her to participate.

- Hospitals are paid $10 for every eligible case reported to the NC Central Cancer Registry.